IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#9 Amdt. B 09/19/01

In re application of:

Better *et al.*

Appl. No. 09/610,838

Filed: July 6, 2000

For: **Fusion Proteins And Polynucleotides Encoding Gelonin Sequences**

Art Unit: 1643

Examiner: A. Salimi

Atty. Docket: 0610.099000A/MAC

Amendment and Reply Under 37 C.F.R. § 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In reply to the Office Action of March 14, 2001, the period for responding to which has been extended three months (from June 14, 2001, to September 14, 2001), by the accompanying petition and payment of fees, Applicants submit the following amendments and remarks. This Amendment is provided in the following format:

(A) A clean version of each replacement paragraph/section/claim along with clear instructions for entry;

(B) Starting on a separate page, appropriate remarks and arguments. 37 C.F.R. § 1.111 and MPEP 714; and

(C) Starting on a separate page, a marked-up version entitled: "Version with markings to show changes made."

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a),

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and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

In the Specification

At page 1, paragraph 1, substitute the following paragraph for the pending paragraph.

This is a continuation of U.S. Application No. 09/136,389, filed August 18, 1998, which is a continuation of U.S. Application No. 08/646,360, which is the U.S. National Phase of PCT/US94/05348, internationally filed May 12, 1994, which is a continuation-in-part of U.S. Application No. 08/064,691, filed May 12, 1993 (now abandoned), which is a continuation-in-part of U.S. Application No. 07/988,430, filed December 9, 1992 (now U.S. Patent No. 5,416,202), which is a continuation-in-part of U.S. Application No. 07/901,707 filed June 19, 1992 (now U.S. Patent No. 5,376,546), which is a continuation-in-part of U.S. Application No. 07/787,567, filed November 4, 1991 (now abandoned).

Remarks

1. The status of the claims

Claims 1- 17 are pending in this application.

2. The amendments

The specification has been amended to refer to correct the recitation of the priority documents.

3. Miscellaneous - Claim to Priority

At page 2 of the Office Action, the Examiner states that "Applicant's claim for 119 benefit to PCT/US92/09487 (November 4, 1992) is noted; however, benefit is denied, since said application was filed more than one year before PCT international application PCT/US94/05348. Applicants respectfully traverse this objection.

Applicants do not claim priority to PCT/US92/09487 and therefore are uncertain as to where the Examiner is referencing when referring to Applicants' claim for benefit of the same. To the extent that a claim for priority to PCT/US92/09487 does exist, Applicants. withdraw the claim of priority to PCT/US92/09487 (November 4, 1992)

It is respectfully submitted that each and every one of the Examiner's objections to Applicants' claim to priority has been overcome. Acknowledgment of the same, and withdrawal of the objection is respectfully requested.

5. The Rejections

a. The rejections under 35 U.S.C. § 112, second paragraph

On Office Action page 3, claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claims the subject matter that Applicants regard as the invention. Applicants respectfully traverse these rejections.

i. "Gelonin"

The Examiner rejects claim 1 as being vague and indefinite stating that the metes and bounds of the gelonin protein are not clear. Applicants respectfully disagree that the metes and bounds are not clear.

Gelonin has a meaning that is commonly known in the art. By saying "gelonin," the artisen immediately knows the claim refers to the well-known type I ribosome inactivating protein (RIP) that could be obtained from seeds of the plant Gelonium multiflorum.

The artisan speaks and discusses "gelonin" with no other functional modifier. In that regard, the Examiner's attention is respectfully directed to the documents in the accompanying Information Disclosure Statement. See, for example, documents:
Accordingly, no additional qualifier need be recited for the artisan to understand the metes and bound of the claim in this regard.

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ii. "Antigen Binding Portion"

The Examiner also rejects claim 1 as being vague and indefinite stating that the antibody specificity has not been defined. Applicants respectfully disagree. The Examiner asks, "What are the antigen binding portions of an antibody, a hormone, a lymphokine or a growth factor?"

As used in the claims, the phrase "an antigen-binding portion" is meant to refer only to "an antigen-binding portion of an antibody." As used in claim 1, the phrase is set off by commas from the surrounding options. Accordingly, the claim does not refer to "an antigen-binding portion" of a hormone, a lymphokine or a growth factor.

Also, as claimed, the phrase "an antigen-binding portion of an antibody" is well-understood in the art to mean any immunoglobulin that contains both the variable domain of a heavy chain and the variable domain of a light chain. The variable domain from one light chain and one heavy chain are required to form a single antigen-combining site.

iii. Is Antibody "Specific for all Cell Surface Receptors"

The Examiner asks, "Is this antibody specific for all the cell surface receptors?" The claim does not recite that the antibody is specific for all the cell surface receptors. The artisan would understand that the targeting sequence, if an antibody, is of sufficient specificity if it allows the internalization of the claimed fusion protein.

iv. The Linker

The Examiner states that claim 4 is indefinite because the intended linker is not defined. Applicants respectfully disagree. The word "linker" is used in its art-recognized sense to mean a sequence that bridges between two other sequences. Specifically, as claimed, the linker is a sequence that is between the gelonin sequence and the targeting sequence. The metes and bounds of the claim are clear. If there is a sequence between the gelonin sequence and the targeting sequence, then that is a linker sequence.

v. "Capable of"

The Examiner states that the term "capable of" in claim 4 is confusing because the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable apprised of the scope of the invention. Applicants respectfully disagree. Recitation of "capable of" as used in claim 4, if anything, adds to the definiteness of the invention as claimed. The artisan who reads claim 4 is informed that the gelonin part of the fusion protein possess enzymatic activity, and the antibody part of the fusion protein possesses antigen binding ability, and the hormone, lymphokine or growth factor part of the fusion protein possess the ability to bind to a cell that has a receptor for such hormone, lymphokine or growth factor, respectively.

The artisan does not need a quantitative value to be assigned to the biological functions in order to be fully informed of the metes and bounds of the claim. In any event, claim 4 must be read in conjunction with claim 1, from which it depends. Claim 1 recites that the targeting sequence allows the internalization of the fusion protein. Therefore, by reading claim 1 with claim 4, the artisan learns that the ability of a desired hormone, lymphokine or

growth factor to bind to its target must be at least sufficient to allow for the internalization of the fusion protein. The metes and bounds are clear.

v. Antibody that is IgM

The Examiner states that claim 6 is unclear and questions what kind of antibody is intended. The examiner questions whether IgM is intended. Applicants respectfully disagree that the claim is unclear.

The claim is directed to a fusion protein that comprises a targeting sequence that allows the internalization of the fusion protein and in which the targeting sequence is an antibody. The fusion protein also comprises the enzymatically active gelonin sequence.

A fusion protein in which the antibody portion was an IgM sequence is intended to be included. There is no reason to assume that a fusion protein in the form of IgM-gelonin would not be active. For example, active conjugates of gelonin with IgM have been reported (see, *e.g.*, *Kaneta*, Y. *et al. Jpn. J. Cancer Res. 89*:583-588 (May, 1998)). Therefore, the claims are not indefinite in this regard.

vi. "An Antigen Binding Portion of an Antibody"

The Examiner states that claim 7 is confusing and indefinite for reciting "an antigen binding portion of an antibody." The Examiner questions whether every subclass of antibodies is intended and also asks "what are the portion or portions?" Applicants respectfully disagree that the claims are indefinite in this regard.

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There is no reason to distinguish subclasses of antibodies when discussing the antigen binding portion of an antibody. The claim is intended to encompass the antigen binding portion from any subclass the artisan desires to use.

Also, as to the portion or portions, as explained above, the phrase "an antigen-binding portion of an antibody" is well-understood in the art to mean a fragment of a full-length antibody that contains at least that portion of an antibody molecule that binds to the antigenic determinant on the antigen - i.e., at least the variable region. The antigen-binding portion is composed of the variable domain amino acid sequences of both light and heavy chains. The variable region from one light chain and one heavy chain are required to form a single antigen-combining site.

Applicants respectfully submit that each and every one of the rejections under 35 U.S.C. §112, second paragraph, has been obviated by the discussion above. Accordingly, this rejection can be withdrawn. The same is believed proper, and is respectfully requested.

b. The rejection under the judicially created doctrine of obviousness type double patenting over U.S. 5,837,491

On Office Action page 5, claims 1-17 are rejected under the judicially created doctrine of obviousness type double patenting over claims 1-3 of U.S. 5,837,491 (herein "the '491 patent"). Applicants respectfully traverse this rejection.

Without acquiescing to the obviousness analysis in regard to the remaining part of the rejection, and solely in the interests of advancing prosecution in this matter, Applicants will submit a terminal disclaimer. Accordingly, this rejection is believed moot.

c. The rejection under the judicially created doctrine of obviousness type double patenting over U.S. 6,146,850

On Office Action page 5, claims 1-17 are rejected under the judicially created doctrine of obviousness type double patenting over claims 1-3 of U.S. 6,146,850 (herein "the '850 patent"). Applicants respectfully traverse this rejection.

Without acquiescing to the obviousness analysis in regard to the remaining part of the rejection, and solely in the interests of advancing prosecution in this matter, Applicants will submit a terminal disclaimer. Accordingly, this rejection is believed moot.

d. The rejection under the judicially created doctrine of obviousness type double patenting over U.S. 6,146,631

On Office Action page 5, claims 1-17 are rejected under the judicially created doctrine of obviousness type double patenting over claims 1-3 of U.S. 6,146,631 (herein "the '631 patent"). Applicants respectfully traverse this rejection.

The claims of U.S. 6,146,631 are directed to a method of eliminating a cell in a patient. The instant claims are directed to a gelonin protein. Applicants had received a restriction requirement in U.S. 6,146,631 in which gelonin protein claims were placed in a different group from the claims directed to "a method of eliminating a cell in a patient." In this regard, the Examiner's attention is directed to the file history of U.S. 6,146,631 (see, *e.g.*, the restriction requirement in the Office Action dated October 30, 1998). Accordingly, no terminal disclaimer is believed necessary and this rejection can be withdrawn.

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e. The rejection under the judicially created doctrine of obviousness type double patenting over U.S. 5,756,699

On Office Action page 5, claims 1-17 are rejected under the judicially created doctrine of obviousness type double patenting over claims 1-3 of U.S. 5,756,699 (herein "the '699 patent"). Applicants respectfully traverse this rejection.

Without acquiescing to the obviousness analysis in regard to the remaining part of the rejection, and solely in the interests of advancing prosecution in this matter, Applicants will submit a terminal disclaimer. Accordingly, this rejection is believed moot.

Conclusion

In view of the discussion above it is believed that the present application is now in condition for immediate allowance. Early notice to this effect is earnestly solicited. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: Sept. 14, 2001

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Version with markings to show changes made.

At page 1, paragraph 1, has been amended as follows.

This is a [Continuation] continuation of U.S. Application No. 09/136,389, filed August 18, 1998[.], which [This application] is a continuation of [co-pending] U.S. [Patent] Application [Serial] No. 08/646,360, which is the U.S. National Phase of PCT/US94/05348, internationally filed May 12, 1994, which is a continuation-in-part of U.S. [Patent] Application [Serial] No. 08/064,691, filed May 12, 1993 (now abandoned), which is a continuation-in-part of U.S. [Patent] Application [Serial] No. 07/988,430, filed December 9, 1992 (now U.S. Patent No. 5,416,202), which is [in turn] a continuation-in-part of U.S. [Patent] Application [Serial] No. 07/901,707 filed June 19, 1992 (now U.S. Patent No. 5,376,546), which [in turn] is a continuation-in-part of U.S. [Patent] Application [Serial] No. 07/787,567, filed November 4, 1991 (now abandoned).